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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61B 17/36 — A1

(11) International Publication Number: WO 96/00038

(43) International Publication Date: 4 January 1996 (04.01.96)

(21) International Application Number: PCT/US95/09047

(22) International Filing Date: 23 June 1995 (23.06.95)

(30) Priority Data:
08/264,458 23 June 1994 (23.06.94) US

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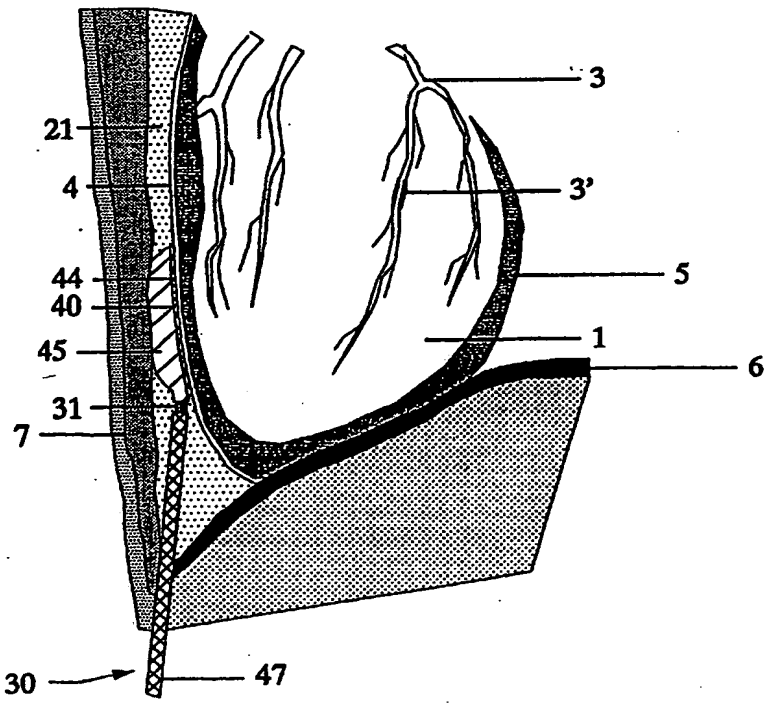
(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, DE, EE, FI, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.

(54) Title: INTRAPERICARDIAL SPACE DRUG DELIVERY APPARATUS AND METHOD

(57) Abstract

This invention is a method and apparatus for delivering a bio-active substance into the pericardial space (1) by percutaneously inserting in the pericardial space the distal end (33) of a distally expandable body (31) comprising a semipermeable membrane (45) having a cross-sectional height to width ratio less than unity when expanded, a cavity (48) provided upon expansion being connected by a lumen (35) in the body (31) that opens proximally exteriorly of the body (31), and introducing a fluid containing a bio-active substance into said lumen under pressure, thereby expanding said distally end of said body (31) within the pericardial space (1), and delivering said fluid through said semipermeable membrane (45) into the pericardial space (1).



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INTRAPERICARDIAL SPACE DRUG DELIVERY APPARATUS AND METHOD

Background Of The Invention

This invention relates to apparatus and methods for the site-specific delivery of bioactive agents into the pericardial space, especially for cardiac and cardiovascular applications.

Coronary arteries, the arteries of the heart, perfuse the cardiac muscle with oxygenated arterial blood. They provide essential nutrients and allow for metabolic waste and gas exchange. These arteries are subject to unremitting service demands for continuous blood flow throughout the life of the patient. A severe proximal coronary artery stenosis with endothelial injury induces cyclic coronary flow reductions ("CFR's"). These are periodic or spasmodic progressive reductions in blood flow in the injured artery. Episodes of CFR's are correlated to clinical acute ischemic heart disease syndromes, which comprise unstable angina, acute myocardial infarction and sudden death. The common pathophysiologic link is endothelial injury with vasospasm and/or thrombus formation.

Coronary artery disease is the leading cause of death today. Historically, the treatment of advanced atherosclerotic coronary artery disease (i.e., beyond that amenable to therapy via medication alone) has involved cardiac surgery in the form of a coronary artery bypass graft ("CABG"). The patient is placed on cardiopulmonary bypass (heart-lung machine) and the heart muscle is temporarily stopped (cardioplegia). Repairs are then surgically affected on the heart in the form of detour conduit grafted vessels (vein or artery graft) providing blood flow around the coronary artery obstruction(s). While CABG surgery has been shown to be effective, it carries with it inherent surgical risk and requires a recuperation period of several weeks. During 1992, approximately 290,000 patients underwent CABG surgery in the United States alone and, in addition, it is estimated that 160,000 underwent coronary thrombolysis therapy, where a clot dissolving agent is injected intravenously or intracoronary to reopen the thrombosed vessel and reduce the incidence of myocardial infarction and sudden death.

A major advance in the treatment of atherosclerotic coronary artery disease occurred in the late 1970's with introduction of the less-invasive percutaneous transluminal coronary angioplasty ("PTCA") procedures. The PTCA technique involves the retrograde introduction, from an artery in the leg or arm, up to the area of coronary vascular stenosis, of a catheter with a small dilating balloon at its tip. The catheter is advanced through the arteries via direct

fluoroscopic guidance and passed across the luminal narrowing of the vessel. Once in place the catheter balloon is inflated for a short period of time. This results in mechanical deformation of the lesion or vessel with a subsequent increase in the cross-sectional area. This in turn reduces obstruction and transluminal pressure gradients, and increases blood flow through the coronary artery. PTCA or angioplasty is a term that now may include other percutaneous transluminal methods of decreasing stenosis within a blood vessel, and includes not only balloon dilation, but also thermal ablation and mechanical atherectomy with shaving, extraction or ultrasonic pulverization of the lesion. During 1992 in the United States, it is estimated that some 400,000 patients underwent coronary angioplasty procedures.

Despite the major therapeutic advances in the treatment of coronary artery disease represented by thrombolytic therapy, CABG operations and PTCA procedures, the success of these measures has been hampered by the development of vessel renarrowing or reclosure, most significantly in patients undergoing thrombolysis and angioplasty procedures. Abrupt vessel occlusion or early restenosis may develop during a period of hours to days post-procedure due to vasospasm and/or platelet thrombus formation at the site of vessel injury. The more common and major limitation, however, is a development of progressive reversion of the diseased vessel to its previous stenotic condition, negating any gains achieved from the procedure. This gradual renarrowing process is referred to as restenosis or intimal hyperplasia. Restenosis is a reparative response to endovascular injury after angioplasty and in vein grafts following vessel bypass surgery. The sequence of events is similar to that described above for unstable lesions associated with endothelial injury, progressing through the process of platelet aggregation, vasoconstriction, thrombus formation, PDGF release, smooth muscle cell proliferation, and thrombus organization.

Clinical studies indicate that thrombolytic therapy is ineffective in about 20% of the treated patients and that 20% of those patients initially responding to therapy develop vessel rethrombosis within one week. Clinical studies also indicate that significant restenosis occurs in about 40% of the PTCA patients within six months and in about 20% of the CABG patients within one year. This complication results in increased morbidity, need for repeating the procedure, and escalating medical costs.

At present, no therapy is know that consistently prevents the major clinical problem of vascular restenosis. Intravenous medications have been tried as a means to prevent PTCA restenosis and other coronary disease syndromes. PGE_1, PGI_2, prostacyclin, sodium

nitroprusside and the other organic nitrates are among various possible medications that have been systemically administered. The difficulty with systemic infusion of PGE_1, PGI_2, prostacyclin, sodium nitroprusside and the other organic nitrates is that, in dosages high enough to provide signs of beneficial cardiac effect, the potent vasodilator and antiplatelet effects of these bioactive agents also produce systemic side effects of bleeding and hypotension. No know therapy consistently prevents acute coronary thrombosis and chronic vascular restenosis while reducing the systemic side-effects of bleeding and hypotension. See, *"Prevention of restenosis after percutaneous transluminal coronary angioplasty: The search for a 'magic bullet'"*, Hermans W., et al., AMER. HEART J., 122:171, 1991; and *"Clinical trials of restenosis after coronary angioplasty"*, Popma J., et al., CIRC., 84:1426, 1991.

Recently, site-specific drug delivery to the arterial wall has become a new strategy for the treatment of vascular diseases, including vessel restenosis following PTCA. These drug delivery systems include: (1) intravascular devices for site-specific (coronary artery) drug delivery comprising double-balloon catheters, porous balloon catheters, microporous balloon catheters, channel balloon catheters, balloon over stent catheters, hydrogel coated balloon catheters, iontophoretic balloon catheters and stent devices; (2) periadventitial and epicardial drug delivery devices, requiring surgical implantation, which include drug-eluting polymer matrices and a iontophoretic patch device; and (3) intramural injection of drug-eluting microparticles. All of these methods are limited by certain problems including additional trauma to the vessel wall, rapid washout of drug, need for invasive insertion, and/or use of therapeutic agents having a single mechanism of action. See, *"Effect of controlled adventitial heparin delivery on smooth muscle proliferation following endothelial injury"*, Edelman E., et al., PROC. NATL. ACAD. SCI., 87:3773, 1990; *"Localized release of perivascular heparin inhibits intimal proliferation after endothelial injury without systemic anticoagulation"*, Okada T., et al., NEUROSURGERY, 25:892, 1989; *"Iontophoretic transmyocardial drug delivery: A novel approach to antiarrhythmic drug therapy"*, Avitall B., et al., CIRC., 85:1582, 1992; *"Direct intraarterial wall injection of microparticles via a catheter: A potential drug delivery strategy following angioplasty"*, Wilensky R., et al., AMER. HEART J., 122: 1136, 1991; *"Local anticoagulation without systemic effect using a polymer heparin delivery system"*, Okada T., et al., STROKE, 19:1470, 1988.

The pericardial sac surrounds the heart like a glove enfolds a hand, and the pericardial space is naturally fluid-filled. The normal pericardium functions to prevent dilatation of the chambers of the heart, lubricates the surfaces of the heart, and maintains the heart in a fixed

geometric position. It also provides a barrier to the spread of infection from adjacent structures in the chest, and prevents the adhesion of surrounding tissues to the heart. The normal pericardial space is small in volume and the fluid film within it is too thin to functionally separate the heart from the pericardium. It has been observed that when fluid is injected into the pericardial space it accumulates in the atrioventricular and interventricular grooves, but not over the ventricular surfaces.

Intrapericardial injection of drugs has been used for the treatment of malignant or loculated pericardial effusions in man. Drugs that have been injected into the pericardial space include antibiotic, antineoplastic, radioactive and fibrinolytic agents. This method of site-specific drug delivery has been shown to be effective in attaining higher, longer-lasting drug levels in the pericardial fluid with lower plasma concentrations and less systemic toxicity. It has been reported that no major complications were associated with the intrapericardial drug infusion catheter and that it was possible to repeat the procedure without difficulty. See, *"Intrapericardial instillation of platin in malignant pericardial effusion"*, Fiorentino M., et al., CANCER, 62:1904, 1988; and *"Use of streptokinase to aid drainage of postoperative pericardial effusion"*, Cross J., et al., BRIT. HEART J., 62:217, 1989.

Intrapericardial drug delivery has not been clinically utilized for heart-specific treatments where pericardial pathology is normal, however, because the pericardial space is normally small and very difficult to access without invasive surgery or risk of cardiac injury by standard needle pericardiocentesis techniques. The pericardiocentesis procedure is carried out by experienced personnel in the cardiac catheterization laboratory, with equipment for fluoroscopy and monitoring of the electrocardiogram. Complications associated with needle pericardiocentesis include laceration of a coronary artery or the right ventricle, perforation of the right atrium or ventricle, puncture of the stomach or colon, pneumothorax, arrhythmia, tamponade, hypotension, ventricular fibrillation, and death. The complication rates for needle pericardiocentesis are increased in situations where the pericardial space and fluid effusion volume is small (i.e., the pericardial size is more like normal).

Chin et al have described a method and apparatus for accessing the pericardial space for the insertion of implantable defibrillation leads *[U.S. Patent No. 5,071,428]*. The method required gripping the pericardium with a forceps device and cutting the pericardium with a scalpel (pericardiotomy) under direct vision through a subxiphoid surgical incision.

Summary Of The Invention

It is an object of this invention to provide apparatus and methods for introducing bioactive substances or drugs into the pericardial space for cardioactive or cardiovascular active effect without invasion of the vascular system.

An object of this invention is to provide nonsystemic, site-specific and time extended administration of bioactive substances at low dosages effective to achieve a desired treatment effect and localized so as not to generalize the effect systemically.

These and other objects and benefits of our invention will become apparent from the description of our invention that now follows.

Our invention provides an apparatus for percutaneously delivering a bioactive substance into the pericardial space, comprising an elongate body having a distal end expandable to a vessel having a cross sectional height-to-width ratio of about 0.5 or less, preferably about 0.25 or less and having pores opening to the exterior of the vessel from a chamber in the vessel provided upon the expansion, the chamber being connected by a lumen in the body that opens exteriorly at a proximal segment of the body for introduction thereinto of a pressurized fluid. The vessel may comprise a semi-permeable membrane in which the pores are microporous.

Relatedly our invention comprises a method of delivering a bioactive substance into the pericardial space. The invention includes transpericardially and intrapericardially delivering the bioactive substance. For intrapericardial delivery it comprises percutaneously inserting in the pericardial space the distal end of a distally expandable body comprising a semi-permeable membrane having a cross sectional height-to-width ratio less than unity when expanded, a cavity provided upon expansion being connected by a lumen in the body that opens proximally exteriorly of the body, and introducing a fluid containing a bioactive substance into the lumen under pressure, thereby expanding the distally end of the body within the pericardial space and delivering the fluid through the semi-permeable membrane into the pericardial space.

For transpericardial delivery it comprises percutaneously inserting over the pericardium the distal end of a distally expandable body having a cross sectional height-to-width ratio less than unity when expanded and pores opening to the exterior of the distal end from a cavity provided upon expansion of the distal end, the cavity being connected by a lumen in the body that opens proximally exteriorly of the body, and introducing a fluid containing a bioactive substance into the lumen under pressure, thereby expanding the distal end of the body to press it against the pericardium and deliver the fluid through the pores onto the pericardium.

In one particular aspect of our invention, the apparatus provides transpericardial delivery of a bioactive substance into the pericardial space employing an iontophoretic drive, with apparatus that comprises an elongate body having a distal end expandable to a vessel having a cross sectional height-to-width ratio of about 0.5 or less, preferably about 0.25 or less with a charge plate thereon in electroconductive contact with an external iontophoretic pad on the charge plate, the pad containing a bioactive substance, the plate being connected to a first lead. with an electrode adjacent the periphery of the pad electrically insulated from the pad and charge plate and connected to a second lead, the first and second leads being contained in the body and exiting the body in a proximal segment thereof, the expandable distal end being connected by a lumen in the body that opens exteriorly at a proximal segment of the body for introduction thereinto of a pressurized fluid.

Thus the invention includes a method of transpericardially delivering a bioactive substance into the pericardial space of a mammal, which comprises percutaneously inserting over the pericardium the distal end of a distally expandable body having an external iontophoretic pad containing a bioactive substance and in electroconductive contact with a radially inward charge plate connected to a first lead with an electrode adjacent the periphery of the pad electrically insulated from the pad and charge plate and connected to a second lead, expanding the distally end of the body to press the iontophoretic pad against the pericardium, and supplying voltage to the first lead to establishes an electrical circuit with the second electrode and iontophoretically drive the bioactive substance from the pad into the pericardium.

Brief Description Of The Drawings

The present invention may be more completely and easily understood when taken in conjunction with the accompanying drawings, in which:

FIG. 1 schematically shows a transpericardial nitrovasodilator drug delivery catheter in place for use in accordance with this invention.

FIG. 2 schematically shows a longitudinal section of a portion of the transpericardial nitrovasodilator drug delivery catheter of FIG. 1.

FIG. 3 schematically shows a cross section of the portion of the transpericardial nitrovasodilator drug delivery catheter of FIG. 2.

FIG. 4 schematically shows a bottom view of a distal portion of the transpericardial nitrovasodilator drug delivery catheter of FIG. 1.

FIG. 5 schematically shows a longitudinal section of an intrapericardial drug delivery catheter for delivery of gaseous bioactive substance to epicardial coronary arteries in accordance with this invention, schematically connected with a gas supply and control system.

FIG. 6 schematically shows a cross section of a proximal part of the intrapericardial drug delivery catheter of FIG. 5.

FIG. 76 schematically shows a cross section of a distal part of the intrapericardial drug delivery catheter of FIG. 5.

FIG. 8 schematically shows an iontophoretic transpericardial drug delivery catheter in place for use in accordance with this invention.

FIG. 9 schematically shows a longitudinal section of a portion of the iontophoretic transpericardial drug delivery catheter of FIG. 8.

FIG. 10 schematically shows a cross section of the portion of the iontophoretic transpericardial drug delivery catheter of FIG. 8.

Detailed Description Of The Preferred Embodiment

Referring to FIGS. 1-4, an epipericardial drug distributing catheter apparatus 30 is illustrated for distribution of a liquid carrying a bioactive drug onto the pericardium for transpericardial delivery of the bioactive drug. The apparatus comprises an elongated catheter body 31 having a proximal segment 32 and distal segment 33. The catheter body 31 includes at least one lumen 35 extending thereinto and exiting the catheter body through a plurality of radially extending first passages 38 in distal segment 33. A balloon 45 is mounted to at least a portion of the exterior of the catheter body distal segment and envelopes first passages 38, providing a cavity 48 between balloon 45 and the distal segment portion containing passages 38, so that passages 38 open into the cavity. A catheter sheath 47 having a distal extremity surrounding at least the distal segment 33 of the catheter body 31. Upon extension of distal segment 33 beyond sheath 47 as shown in FIGS. 1-4, balloon 45 is able to expand. Balloon 45 has a height-to-width cross sectional ratio of less than unity when expanded, as shown, when outside a catheter, preferably a height-to-width cross sectional ratio of about 0.5 or less,

preferably about 0.25 or less. Balloon 45 preferably when expanded has a width from about one to about four inches (or about 2.5 cm to about 10 cm) and a height of about 0.4 inch or less (about 1.0 cm or less, typically about 0.625 cm). Typically the diameter of sheath 47 is about 0.4 inch or less (about 1.0 cm or less, typically about 0.625 cm). Thus upon expansion the balloon is significantly wider than it is high, and may have a generally pancake shape.

A second lumen 34 catheter body 31 extends to a plurality of passages 36 radially spaced from the first passages 38 and connect second lumen 34 to the exterior of the distal segment 33. Balloon 45 is mounted to the portion of the exterior surface of the catheter body distal segment above the second passages 36 so as not to cover them. Thus, percutaneous insertion and upon extension of distal segment 33 beyond sheath 47 and over the pericardium, a fluid introduced through first lumen 35 expands the balloon to press the radially opposite surface of the distal segment against the pericardial tissue surface and a pressurized fluid introduced into the second lumen exits the catheter onto the surface against which the distal segment is pressed. However, it is preferred to envelop passages 36 within a vessel to more expediently control flow onto the pericardium. Thus apparatus 30 further comprises an expandable vessel 40 mounted to an exterior surface of the distal segment of the catheter body adjacent and radially opposite balloon 45 and over the second passages 36, thereby providing a vessel chamber 42 between the vessel and the radially adjacent exterior surface of distal segment 33 into which the second passages open. Vessel 40 has a height-to-width cross sectional ratio of less than about unity when expanded and has pores 43 to allow passage of fluid from vessel 40 under influence of a pressure gradient across pores 43, thereby providing flow communication from second lumen 34 through second passages 36 into vessel chamber 42 and out of vessel chamber 42 through pores 43, whereby upon percutaneous introduction of the distal segment 33, a pressurized fluid introduced through first lumen 35 expands balloon 45 to press vessel 40 against the pericardial tissue surface, and a fluid introduced under pressure into second lumen 34 passes through the pores 43 of vessel 40 onto the surface against which the distal segment is pressed. Expanded vessel 40 preferably has a height-to-width cross sectional ratio is 0.5 or less, preferably about 0.25 or less. Vessel 40 preferably when expanded has a width from about one to about four inches (or about 2.5 cm to about 10 cm) and a height of about one-fourth inch (or about 0.625 cm) or less. Thus upon expansion vessel 40 is significantly wider than it is high, and may have a generally pancake shape. Suitably vessel 40 comprises a semi-permeable membrane and the pores are microporous.

In use of drug delivery catheter 30, sheath 47 with catheter 31 nested therein is advanced within an introducer under the xiphod process of the sternum 7 into the mediastinum 21 of the thoracic cavity 22 to a position between pericardium 4 and the inner chest wall, as shown in FIG. 1. The distal end of catheter body 31 is advanced from sheath 47 to extend the vessel 40 and the balloon 45 beyond the distal extremity of sheath 47 and dispose exterior portion 44 of vessel 40 against pericardium 4 and orient balloon 45 facing the inner chest wall. A gas or liquid fluid, suitably air, is introduced through first lumen 35 and passes therethrough into balloon 45, inflating balloon. This expands balloon 45 into contact against the inner chest wall of the mediastinum. The relatively wider than vertical aspect of balloon 45 assists in stabilizing the distal segment from rotation. Inflation also causes balloon 45 to press exterior portion 44 of vessel 40 against the surface of pericardium 4. A liquid fluid is introduced into first lumen 34 and passes therethrough into vessel 40, expanding vessel 40 predominately laterally. The liquid passes from vessel chamber 42 through the outlets 43 and emerges therefrom onto the surface of pericardium 4 for transpericardial passage of a drug (bioactive drug) in solution in the liquid and entry of the drug into the pericardial fluid bathing the heart, from which it suitably comes into contact with the coronary arteries for migration into the vessel wall for cardiovascular effect.

Referring to FIGS. 5-7, an apparatus 50 for intrapericardial delivery of gaseous nitric oxide to the epicardial coronary arteries in accordance with our invention is illustrated schematically. It comprises an elongated catheter body 51 having a proximal segment 52 and a distal segment 53, the catheter body including at least one lumen 55 extending thereinto and exiting the catheter body through at least one first passage 58 in the distal segment, and a balloon 60 mounted to at least a portion of the exterior of the catheter body distal segment and enveloping the first passage 58, providing a cavity 62 between the balloon and the distal segment, the first passage 58 opening into cavity 62. Balloon 60 preferably has a height-to-width cross sectional ratio of less than unity when expanded, more preferably, a height-to-width cross sectional ratio of about 0.5 or less, preferably about 0.25 or less, and comprises a semi-permeable membrane suitable for diffusion therethough of a fluid supplied under pressure through the lumen to the passage. Apparatus 50 comprises a second lumen 54 that extends through the distal end 53 of catheter 51 for receiving a guidewire 57 therethrough. A tube 59 surrounding at least a portion of catheter body 51 creates a passageway 65 therebetween. An introducer 63 surrounds at least a portion of catheter body 51 for introduction of distal segment

53 into the thoracic cavity and extension of balloon 60 beyond the distal extremity of sheath 63 for disposition exteriorly of the sheath on guidewire 57.

In use of apparatus 50 for intrapericardial delivery of gaseous nitric oxide to the epicardial coronary arteries in accordance with our invention, gaseous nitric oxide supplied by tank 70 is carried by conduit 71 controlled by microvalve 72 actuated by a solenoid 73 responsive to a pressure differential diaphragm 74 and is introduced into catheter apparatus 50, of which distal segment 53 has been introduced through the pericardium 4 through introducer 63. The nitric oxide gas flows through passageway 65 and passes into balloon 60 which it inflates. The nitric oxide resident in balloon cavity 62 passes from cavity 62 through the gas permeable membrane of balloon 60 and enters the pericardial fluid bathing the coronary arteries for treatment of them. Gas within balloon cavity 62 has an exit passage from balloon cavity 62 through openings 58 for withdrawal from the balloon through lumen 55 into a gas return conduit 75 under the force of withdrawal pump 76.

Referring to FIGS. 8-10, an apparatus for iontophoretic delivery of a bioactive drug onto the pericardium for transpericardial delivery of the bioactive drug is depicted schematically. The device is similar to the device illustrated in FIGS. 1-3, and corresponding numbers indicate similar structure. An expandable vessel 40 mounted to an exterior surface of said distal segment of said catheter body adjacent and radially opposite balloon 45 and having a height-to-width cross sectional ratio of less than about unity when expanded comprises an expandable iontophoretic pad 82 containing a bioactive substance. The second lumen 34 (see FIG. 10) carries electrical leads 80, 81. Voltage carrying lead 80 is connected to a charge plate 83 in front of which is pad 82 containing a repository of a bioactive drug. Pad 82 is attached to the outer surface 41 of distal segment 33. Circumscribing the perimetry of pad 82 is negative electrode 84, electrically insulated from charge plate 83 and pad 82 by electrode insulators 85, 86. Negative electrode 84 is coupled to the ground of lead 81. When pad 82 is placed in contact with the pericardium 4 and plate 83, a charge is provided over lead 80 to charge plate 83. An electric field is established between charge plate 83 and negative electrode 84. This electric field penetrates through the pericardium as it flows from plate 83 to electrode 84. The field passes through bioactive drug pad 82, and charged bioactive drug molecules contained within pad 82 migrate from pad 82 and through pericardium 4 as the electric field traverses the pericardial membrane. The charge supplied to plate 83 is sufficient to establish the iontophoretic circuit, but insufficient to disturb the transmission of the cardiac impulse through the heart.

By use of the apparatus of this invention coronary arteries of the heart can be treated by application of therapeutic substances to the exterior surface of the heart. Cardio-active and cardiovascular-active drugs for intrapericardial delivery can include vasodilator, antiplatelet, anticoagulant, thrombolytic, anti-inflammatory, antiarrhythmic, inotropic, antimitotic, angiogenic, antiatherogenic and gene therapy agents. As already mentioned, fluid injected into the pericardial space accumulates in the atrioventricular and interventricular grooves. Since the epicardial coronary arteries are located in the grooves of the heart, a bioactive therapeutic substance delivered into the pericardial space through the methodology and devices of this invention can accumulate and be concentrated over the coronary blood vessels.

Having now described in detail the methodology of our invention, those in the art will appreciate more than merely the detailed means described for implementing the invention, and our invention is not meant to be limited merely to these detailed implementations, but to all implementations comprehended by our claims within the spirit of our invention.

We claim:

1. An apparatus for percutaneously delivering a bioactive substance into the pericardial space, comprising an elongate body having a distal end expandable to a vessel having a cross sectional height-to-width ratio of about 0.5 or less and having pores opening to the exterior of the vessel from a chamber in said vessel provided upon said expansion, said chamber being connected by a lumen in the body that opens exteriorly at a proximal segment of the body for introduction thereinto of a pressurized fluid.

2. The apparatus of claim 1 in which said vessel comprises a semi-permeable membrane and said pores are microporous.

3. An apparatus for transpericardially delivering a bioactive substance into the pericardial space, comprising an elongate body having a distal end expandable to a vessel having a cross sectional height-to-width ratio of about 0.5 or less with a charge plate thereon in electroconductive contact with an external iontophoretic pad on the charge plate, said pad containing a bioactive substance, said plate being connected to a first lead, with an electrode adjacent the periphery of said pad electrically insulated from said pad and charge plate and connected to a second lead, said first and second leads being contained in said body and exiting said body in a proximal segment thereof, said expandable distal end being connected by a lumen in the body that opens exteriorly at a proximal segment of the body for introduction thereinto of a pressurized fluid.

4. An apparatus for percutaneous introduction, comprising

an elongated catheter body having a proximal and distal segment,

said catheter body including at least one lumen extending thereinto and exiting said catheter body through at least one first passage in said distal segment, and

a balloon mounted to at least a portion of the exterior of said catheter body distal segment and enveloping said first passage, providing a cavity between the balloon and the distal segment, said first passage opening into said cavity, said balloon having a height-to-width cross sectional ratio of less than unity when expanded.

5. The apparatus of claim 4 in which said balloon has a height-to-width cross sectional ratio of about 0.5 or less.

6. The apparatus of claim 4 in which said balloon comprises a semi-permeable membrane suitable for diffusion therethough of a fluid supplied under pressure through said lumen to said passage.

7. The apparatus of claim 4 in which said balloon when expanded has a width from about 2.5 cm to about 10 cm and a height of about 1 cm or less.

8. The apparatus of claim 4 wherein said first passage exits radially to the long dimension of said catheter body, and further comprising:

a second lumen in said catheter body extending to at least one second passage radially spaced from said first passage and connecting said second lumen to the exterior of said distal segment, said balloon being mounted to said portion of said exterior surface of said catheter body distal segment to not cover said second passage, whereby upon percutaneous introduction of said distal segment, a fluid introduced through said first lumen expands said balloon to press the radially opposite surface of the distal segment against a tissue surface and a pressurized fluid introduced into said second lumen exits the catheter onto said surface against which the distal segment is pressed.

9. The apparatus of claim 8 further comprising:

an expandable vessel mounted to an exterior surface of said distal segment of said catheter body adjacent and radially opposite said balloon and over said second passage, thereby providing a vessel chamber between the vessel and said radially adjacent exterior surface into which said second passage opens, said vessel having a height-to-width cross sectional ratio of less than about unity when expanded and having pores to allow passage of fluid from the vessel under influence of a pressure gradient across the pores, thereby providing flow communication from said second lumen through said second passage into said vessel chamber and out of said vessel chamber through said pores, whereby upon percutaneous introduction of said distal segment, a pressurized fluid introduced through said first lumen expands said balloon to press said vessel of the distal segment against a tissue surface and a fluid introduced under pressure into said second lumen passes through said pores of said vessel onto said surface against which the distal segment is pressed.

10. The apparatus of claim 9 in which said expanded vessel height-to-width cross sectional ratio is 0.5 or less.

11. The apparatus of claim 9 in which said vessel comprises a semi-permeable membrane and said pores are microporous.

12. The apparatus of claim 10 in which said vessel when expanded has a width from about one to about four inches and a height of about one-half inch or less.

13. The apparatus of claim 9 further comprising

a catheter sheath having a distal extremity surrounding at least said distal segment of said catheter body for percutaneous introduction of said distal segment into the mammal and extension of said balloon and said vessel beyond the distal extremity of said sheath for disposition exteriorly of said sheath.

14. The apparatus of claim 4 wherein said first passage exits radially to the long dimension of said catheter body, and further comprising:

a second lumen in said catheter body extending to at least one second passage radially spaced from said first passage and connecting said second lumen to the exterior of said distal segment, said balloon being mounted to said portion of said exterior surface of said catheter body distal segment to not cover said second passage,

an expandable vessel mounted to an exterior surface of said distal segment of said catheter body adjacent and radially opposite said balloon and over said second passage, thereby providing a vessel chamber between the vessel and said radially adjacent exterior surface into which said second passage opens, said vessel having a height-to-width cross sectional ratio of less than about unity when expanded, said vessel comprising an expandable iontophoretic pad containing a bioactive substance adjacent said plate with said plate,

first and second electroconductive leads received in said second lumen,

a charge plate connected to said first lead and adjacent said pad in electroconductive contact therewith, and

an electrode adjacent the periphery of said pad electrically insulated from said pad and charge plate and connected to said second lead.

15. The apparatus of claim 9 in which said vessel height-to-width cross sectional ratio is 0.5 or less.

16. A method of delivering a bioactive substance into the pericardial space of a mammal, which comprises:

percutaneously inserting in the pericardial space the distal end of a distally expandable body comprising a semi-permeable membrane having a cross sectional height-to-width ratio less than unity when expanded, a cavity provided upon expansion being connected by a lumen in the body that opens proximally exteriorly of the body,

introducing a fluid containing a bioactive substance into said lumen under pressure, thereby expanding said distally end of said body within the pericardial space and delivering said fluid through said semi-permeable membrane into the pericardial space.

17. A method of transpericardially delivering a bioactive substance into the pericardial space of a mammal, which comprises:

percutaneously inserting over the pericardium the distal end of a distally expandable body having a cross sectional height-to-width ratio less than unity when expanded and pores opening to the exterior of the distal end from a cavity provided upon expansion of said distal end, said cavity being connected by a lumen in the body that opens proximally exteriorly of the body,

introducing a fluid containing a bioactive substance into said lumen under pressure, thereby expanding said distal end of said body to press it against the pericardium and deliver said fluid through said pores onto the pericardium.

18. A method of transpericardially delivering a bioactive substance into the pericardial space of a mammal, which comprises:

providing an apparatus comprising an elongated catheter body having a proximal and distal segment, said catheter body including at least first and second lumens extending thereinto and exiting said catheter body through separate radially spaced first and second passages in said distal segment, a balloon mounted to at least a portion of the exterior of said catheter body distal segment and enveloping said first passage but not said second passage, thereby affording a balloon cavity between the balloon and said distal segment exterior, said first passage opening into said cavity, and an expandable vessel mounted to an exterior surface of said distal segment of said catheter body adjacent and radially opposite said balloon and over said second passage, thereby affording a vessel chamber between the vessel and said radially adjacent exterior

surface into which said second passage opens, said vessel having pores for passage of fluid therethough to the exterior thereof radially opposite said balloon,

percutaneously introducing said distal segment over the pericardium,

introducing a fluid through said first lumen to expand said balloon to press said vessel of the distal segment against the pericardium, and

introducing a fluid containing a bioactive substance into said second lumen and delivering the fluid onto said pericardium surface from said outlet of said vessel.

19. A method of transpericardially delivering a bioactive substance into the pericardial space of a mammal, which comprises:

percutaneously inserting over the pericardium the distal end of a distally expandable body having an external iontophoretic pad containing a bioactive substance and in electroconductive contact with a radially inward charge plate connected to a first lead with an electrode adjacent the periphery of said pad electrically insulated from said pad and charge plate and connected to a second lead,

expanding said distally end of said body to press said iontophoretic pad against the pericardium, and

supplying voltage to said first lead to establishes an electrical circuit with said second electrode and iontophoretically drive said bioactive substance from said pad into the pericardium.

20. A method of transpericardially delivering a bioactive substance into the pericardial space of a mammal, which comprises:

providing an apparatus comprising an elongated catheter body having a proximal and distal segment, said catheter body including at least first and second lumens extending thereinto and exiting said catheter body through separate radially spaced first and second passages in said distal segment, a balloon mounted to at least a portion of the exterior of said catheter body distal segment and enveloping said first passage but not said second passage, thereby affording a balloon cavity between the balloon and said distal segment exterior, said first passage opening into said cavity, an expandable vessel mounted to an exterior surface of said distal segment of said catheter body adjacent and radially opposite said balloon and over said second passage,

thereby providing a vessel chamber between the vessel and said radially adjacent exterior surface into which said second passage opens, said vessel having a height-to-width cross sectional ratio of less than about unity when expanded, said vessel comprising an expandable iontophoretic pad containing a bioactive substance adjacent said plate with said plate, first and second electroconductive leads received in said second lumen, a charge plate connected to said first lead and adjacent said pad in electroconductive contact therewith, and an electrode adjacent the periphery of said pad electrically insulated from said pad and charge plate and connected to said second lead,

percutaneously introducing said distal segment over the pericardium,

introducing a fluid through said first and second lumens to expand said balloon and vessel to press said pad on the distal segment against the pericardium, and

supplying voltage to said first lead to establishes an electrical circuit with said second electrode and iontophoretically drive said bioactive substance from said pad into the pericardium.

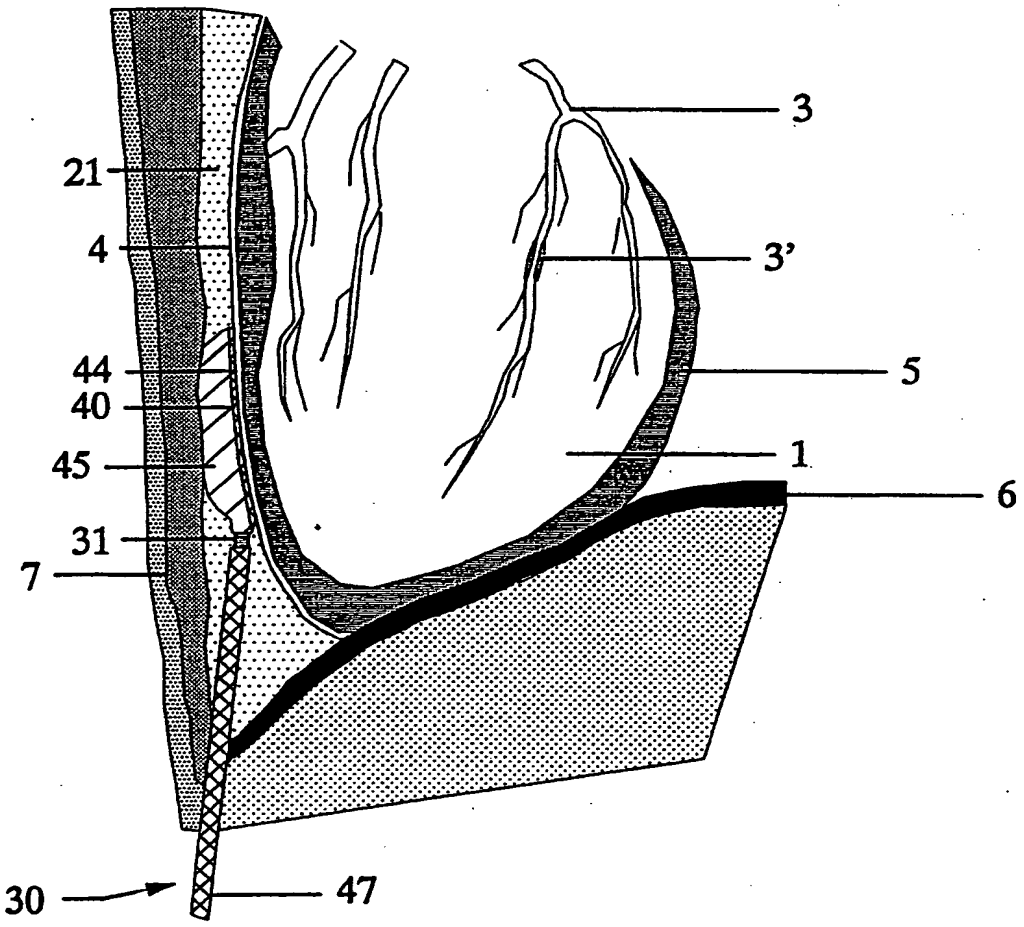

FIG 1

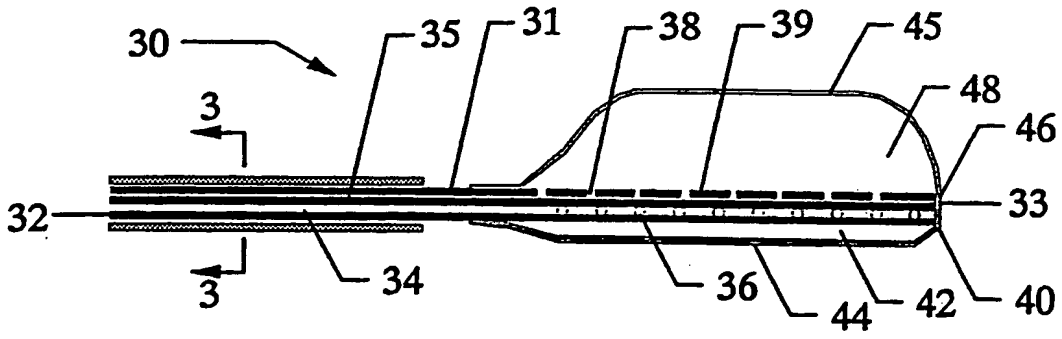

FIG 2

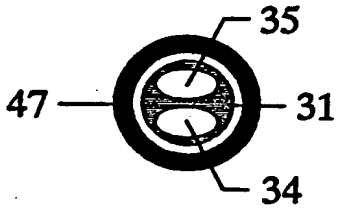

FIG 3

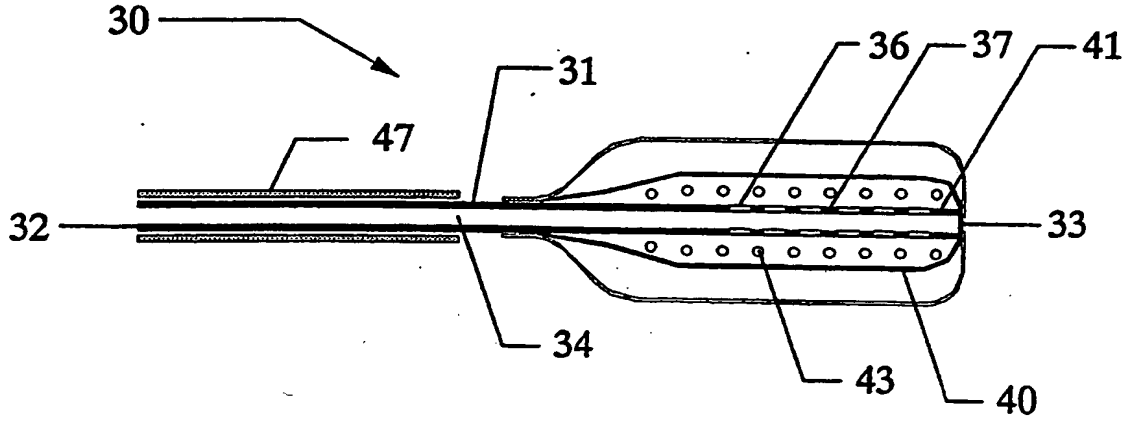

FIG 4

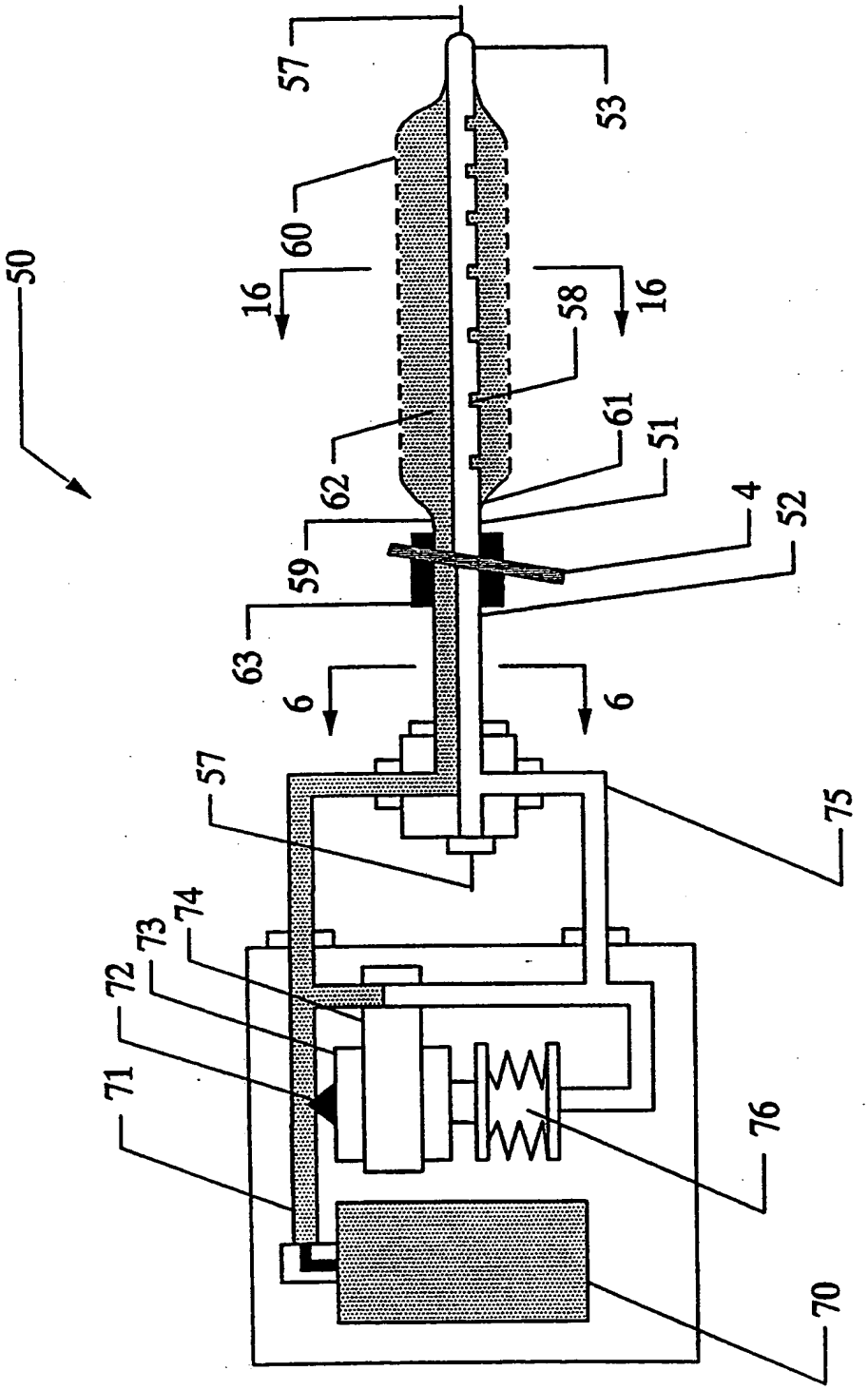

FIG 5

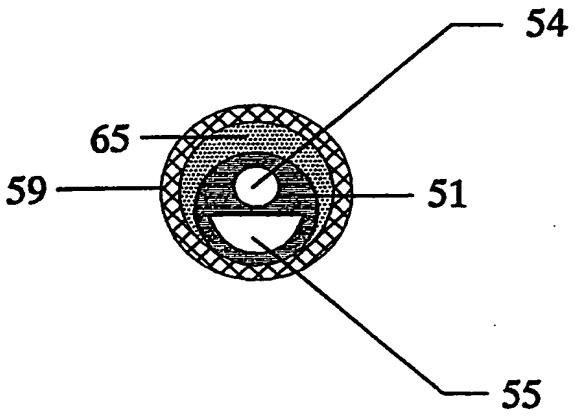

FIG 6

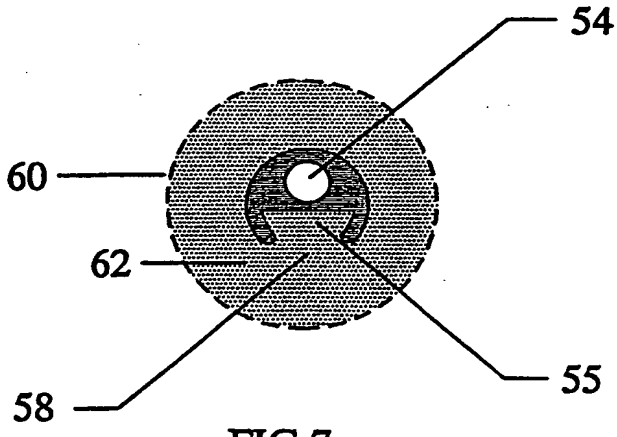

FIG 7

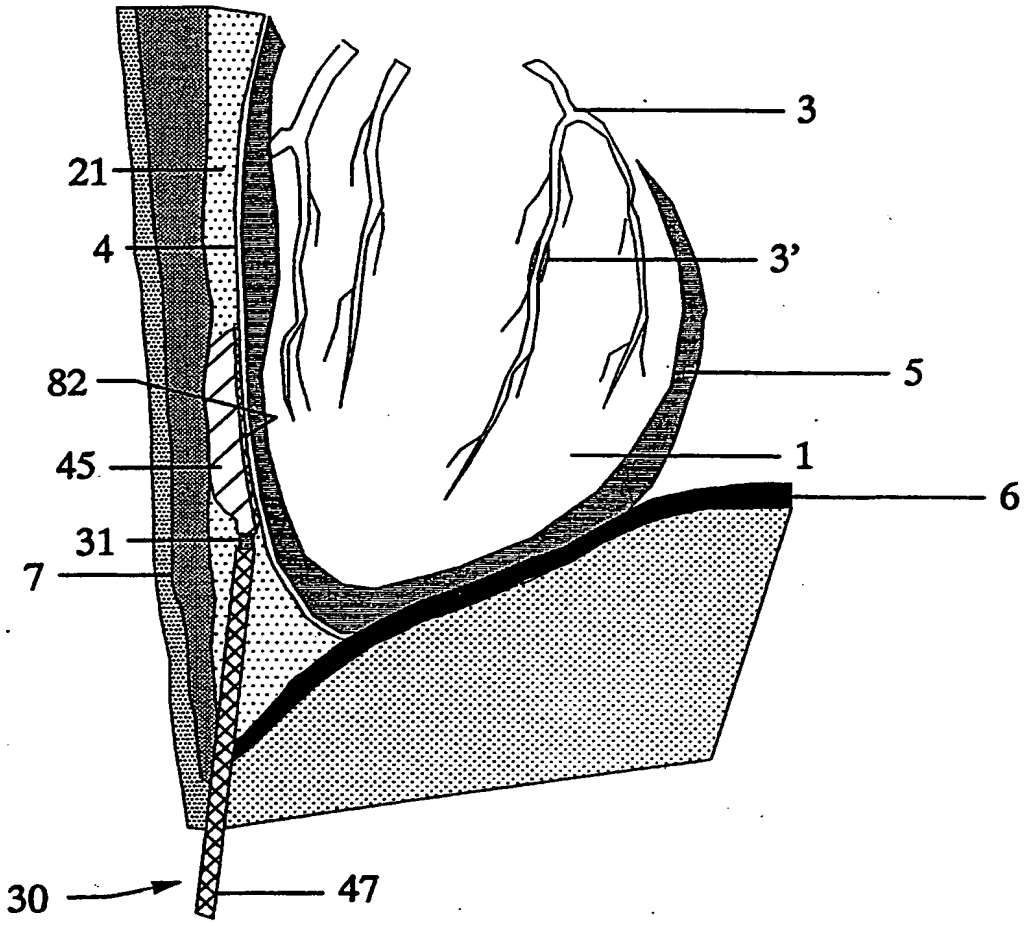

FIG 8

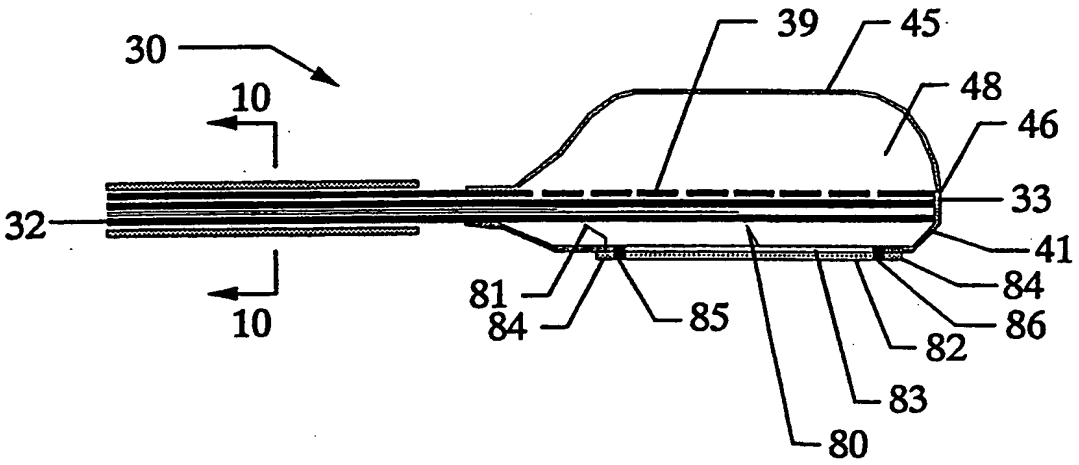

FIG 9

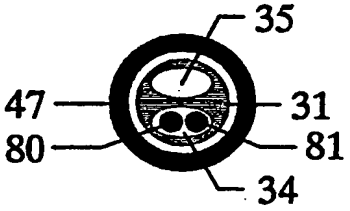

FIG 10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/09047

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 17/36
US CL :128/658; 604/19-22, 51, 96, 101, 890.1, 891.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/658; 604/19-22, 51, 96, 101, 890.1, 891.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS. DIALOG

Search Terms: pericardium, catheter, balloon, and iontophoresis

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US, A, 5,282,785 (SHAPLAND ET AL.) 01 February 1994, see entire document, and note Figs. 5, 7 and 8.	1, 2, 4-13, 15-18, --- 3, 14, 19, 20
A	US, A, 5,236,413 (FEIRING) 17 August 1993, see entire document.	1-20
A	US, A, 5,178,608 (WINTERS) 12 January 1993, note element (70).	1-20
A	US, A, 5,163,905 (DON MICHAEL) 17 November 1992, note Figs. 8 and 9, and element (90).	1-20

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"A" document defining the general state of the art which is not considered to be part of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 SEPTEMBER 1995	29 SEP 1995

Name and mailing address of the ISA/US	Authorized officer
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Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/09047

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,751,924 (HAMMERSCHMIDT ET AL.) 21 June 1988, note Fig. 1 elements (8)(9).	1-20
Y, P	US, A, 5,421,818 (ARENBERG) 06 June 1995, note Figs. 2 and 3, elements (70)(72)(73).	3, 14, 19, 20